DOCKET NO.: BMS-2027 (PH-7176) PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: **Shuang Liu, *et al.*** Confirmation No.: **5136**

Serial No.: **09/899,629** Group Art Unit: 1617

Filing Date: **July 5, 2001** Examiner: **Shengjun Wang**

For: **Stable Radiopharmaceutical Compositions And Methods For Preparation Thereof**

EXPRESS MAIL LABEL NO: EV325723317US
DATE OF DEPOSIT: December 9, 2004

Mail Stop Appeal-Brief Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

APPELLANT'S BRIEF PURSUANT TO 37 C.F.R. § 41.37

This brief is being filed in support of Appellant's appeal from the rejections of claims 19-22, 20-33, and 35-39 dated April 15, 2004. A Notice of Appeal was filed on September 9, 2004, and received in the U.S. Patent Office on September 9, 2004.

1. REAL PARTY IN INTEREST

Bristol-Myers Squibb Company by virtue of the assignment recorded February 11, 2002, at Reel 012607 Frame 0038.

2. RELATED APPEALS AND INTERFERENCES

None.

3. STATUS OF CLAIMS

Claim 1	Withdrawn
Claim 2	Withdrawn
Claim 3	Withdrawn
Claim 4	Withdrawn
Claim 5	Withdrawn
Claim 6	Withdrawn
Claim 7	Withdrawn
Claim 8	Withdrawn
Claim 9	Withdrawn
Claim 10	Withdrawn
Claim 11	Withdrawn
Claim 12	Withdrawn
Claim 13	Withdrawn
Claim 14	Withdrawn
Claim 15	Withdrawn
Claim 16	Withdrawn
Claim 17	Withdrawn
Claim 18	Withdrawn
Claim 19	Rejected and On Appeal
Claim 20	Rejected and On Appeal
Claim 21	Rejected and On Appeal
Claim 22	Rejected and On Appeal
Claim 23	Withdrawn
Claim 24	Withdrawn
Claim 25	Withdrawn
Claim 26	Withdrawn
Claim 27	Withdrawn
Claim 28	Withdrawn
Claim 29	Withdrawn
Claim 30	Rejected and On Appeal
Claim 31	Rejected and On Appeal

Claim 32	Rejected and On Appeal
Claim 33	Rejected and On Appeal
Claim 34	Withdrawn
Claim 35	Rejected and On Appeal
Claim 36	Rejected and On Appeal
Claim 37	Rejected and On Appeal
Claim 38	Rejected and On Appeal
Claim 39	Rejected and On Appeal
Claim 40	Withdrawn
Claim 41	Withdrawn
Claim 42	Withdrawn
Claim 43	Withdrawn
Claim 44	Withdrawn
Claim 45	Withdrawn
Claim 46	Withdrawn
Claim 47	Withdrawn
Claim 48	Withdrawn
Claim 49	Withdrawn
Claim 50	Withdrawn
Claim 51	Withdrawn
Claim 52	Withdrawn
Claim 53	Withdrawn
Claim 54	Withdrawn
Claim 55	Withdrawn
Claim 56	Withdrawn
Claim 57	Withdrawn
Claim 58	Withdrawn
Claim 59	Withdrawn
Claim 60	Withdrawn
Claim 61	Withdrawn
Claim 62	Withdrawn
Claim 63	Withdrawn
Claim 64	Withdrawn

Claim 65	Withdrawn
Claim 66	Withdrawn
Claim 67	Withdrawn
Claim 68	Withdrawn
Claim 69	Withdrawn
Claim 70	Withdrawn
Claim 71	Withdrawn
Claim 72	Withdrawn
Claim 73	Withdrawn
Claim 74	Withdrawn
Claim 75	Withdrawn
Claim 76	Withdrawn
Claim 77	Withdrawn
Claim 78	Withdrawn
Claim 79	Withdrawn
Claim 80	Withdrawn
Claim 81	Withdrawn
Claim 82	Withdrawn
Claim 83	Withdrawn
Claim 84	Withdrawn
Claim 85	Withdrawn
Claim 86	Withdrawn
Claim 87	Withdrawn
Claim 88	Withdrawn
Claim 89	Withdrawn
Claim 90	Withdrawn
Claim 91	Withdrawn
Claim 92	Withdrawn

4. STATUS OF AMENDMENTS

No amendment has been filed subsequent to the final rejection of April 15, 2004.

5. SUMMARY OF INVENTION

The present invention relates to stable radiopharmaceutical compositions for treating patients. Such compositions are preferably administered parenterally to treat or diagnose certain conditions. *See Appellant's Specification* at pages 61-62.

As claimed in Appellant's sole pending independent claim 19, the present invention conceptually comprises a two part composition. In the first part, Formula II, a biological molecule (BM), such as an antibody, an antibody fragment, a peptide, a peptidomimetic, or a non-peptide, is provided for targeting the diseased tissue. This biological molecule is radio-labeled with a radionuclide (RI) (*i.e.*, radioactive atom) for having a diagnostic or therapeutic effect on the tissue. Such an arrangement results in the radioactivity being concentrated in the areas of interest, such as a tumor, as opposed to being dispersed throughout the body, which is desirable for a number of reasons, including safety and efficacy. An optional chelator (Ch) (mainly for use with metallic radionuclides) and an optional linking group (Ln) (useful to resolve steric and pharmacokinetic problems) are also provided.

The second part of the composition is a stabilizer compound, Formula I. The stabilizer compound is defined by recited structure found in claim 19. In the industry, other stabilizing compounds were known, a number of which were listed in Appellant's specification at pages 6, line 30 - 8, line 8. However, none of these meet the recited structure found in claim 19. Moreover, Appellant's specification at page 29, lines 23-31, specifically excludes compounds like gentisic acid and derivatives thereof.

6. ISSUES

Whether the Examiner has demonstrated that Claims 19-22, 30-33, and 35-39 are unpatentable under the judicially created doctrine of obviousness-type double patenting over claims 22, and 28-30 of U.S. Patent No. 6,537,520 (the "Rajopadhye reference") in view of U.S. Patent No. 5,679,318 (the "Vanderheyden reference") and further in view of the abstract of JP 56144060 to Nippon Oils and Fats Co. (the "Nippon Oils and Fats reference").

Whether Claims 19-22, 30-33, and 35-39 are unpatentable under 35 U.S.C. §103(a) over the Rajopadhye reference in view of the Vanderheyden reference and further in view of the Nippon Oils and Fats reference.

Whether the Examiner has demonstrated that Claims 19-22, 30-33, and 35-39 are unpatentable under 35 U.S.C. §103(a) over U.S. Patent No. 5,750,088 (the "Sworin reference") or U.S. Patent No. 5,707,603 (the "Toner reference") in view of the Vanderheyden reference and further in view of the Nippon Oils and Fats reference.

7. GROUPING OF CLAIMS

The claims of each group do **not** stand or fall together. See the Remarks section.

8. REMARKS

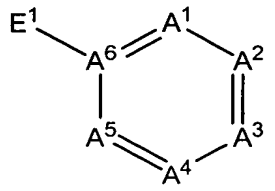
A. ISSUES WITH RESPECT TO INDEPENDENT CLAIM 19

Appellant's Claim 19 is the sole independent claim at issue. It recites a pharmaceutical composition comprising:

(1.) a radiolabeled pharmaceutical agent of the formula (II)

$$RI\text{-}Ch\text{-}L_n\text{-}(BM)_x \qquad (II);\ \text{and}$$

(2.) an effective stabilizing amount of a compound of formula (I):



wherein

RI is ^{99m}Tc, ^{131}I, ^{125}I, ^{123}I, ^{117m}Sn, ^{111}In, ^{97}Ru, ^{203}Pb, ^{67}Ga, ^{68}Ga, ^{89}Zr, ^{90}Y, ^{177}Lu, ^{149}Pm, ^{153}Sm, ^{166}Ho, ^{131}I, ^{32}P, ^{211}At, ^{47}Sc, ^{109}Pd, ^{105}Rh, ^{186}Re, ^{188}Re, ^{60}Cu, ^{62}Cu, ^{64}Cu, ^{67}Cu;

C_h is a metal chelator or is a direct linkage;

L_n is a linking group or is a direct linkage;

each BM is independently an antibody, an antibody fragment, a peptide, a peptidomimetic, or a non-peptide;

x is 1 to about 10;

E^1 is NH_2 or OH;

A^1, A^2, A^3, A^4 and A^5 are each independently N, C(OH) or CR^1;

provided at least one of A^1, A^2, A^3, A^4 and A^5 is not CH;

each R^1 is independently H, $C(O)R^2$, $C(O)OR^2$, $NHC(=O)NHR^2$, $NHC(=S)NHR^2$, $OC(=O)R^2$, $OC(=O)OR^2$, $S(O)_2OR^2$, $C(O)NR^3R^4$, $C(O)NR^3OR^4$, $C(O)NR^2NR^3R^4$, NR^3R^4, $NR^3C(O)R^4$, $PO(OR^3)(OR^4)$, $S(O)_2NR^3R^4$, $S(O)_2NR^2NR^3R^4$, $S(O)_2NR^3OR^4$, C_1-C_{10} alkyl substituted with 0-5 R^5, C_3-C_{10} cycloalkyl substituted with 0-5 R^5, C_2-C_{10} alkenyl substituted with 0-5 R^5, or aryl substituted with 0-5 R^5;

R^2, R^3, and R^4 are each independently H, C_1-C_6 aikyl, C_3-C_6 cycloalkyl, C_1-C_6 alkenyl, benzyl, or phenyl; or R^3 and R^4 together form C_3-C_{10} cycloalkyl or C_3-C_{10} cycloalkenyl, optionally interrupted with O, S, NH, S(=O), $S(O)_2$, P(=O)(OH), C(=O)NH, NHC(=O), NHC(=O)NH, or NHC(=S)NH; and

each R^5 is independently H, NH_2, OH, CO_2H, $C(=O)NH_2$, $C(=O)NHOH$, $C(=O)NHNH_2$, $NHC(=NH)NH_2$, $NHC(=O)NH_2$, $NHC(=S)NH_2$, PO_3H_2, SO_3H, or $S(O)_2NH_2$;

or a pharmaceutically acceptable salt thereof;

provided the compound of formula (I) is not (1) a substituted monohydroxyl aromatic compound; (2) a substituted dihydroxyl aromatic compound, in which the two hydroxyl groups are not adjacent to each other; (3) a substituted monohydroxyl-monoamino aromatic compound, in which the hydroxyl group and amino group are not adjacent to each other; or (4) an ortho, meta, or para aminobenzioc acid.

(Emphasis added).

Whether the Examiner has demonstrated that Claims 19-22, 30-33, and 35-39 are unpatentable under the judicially created doctrine of obviousness-type double patenting over claims 22, and 28-30 of the Rajopadhye reference in view of the Vanderheyden reference and further in view of the Nippon Oils and Fats reference.

Assuming *arguendo* that the Radjopadhye reference provides a compound of Formula II, the Office Action dated Oct. 28, 2003 admits that the Rajopadhye reference "does not expressly claims [*sic*] the stabilizers in the composition or kit." *Id.* at page 3. **In fact, no compounds of Formula I are taught or suggested by the Rajopadhye reference.**

As an aside, the policy concern of a double patenting rejection lies in preventing an improper extension of a patent monopoly by filing multiple applications on obvious variations of the same invention. However, by the Examiner's own admission above, this present invention cannot be an obvious variation of the Rajopadhye reference, because other references are needed to supply its lack of teachings.

Appellant's claim defines the components and states "provided the compound of formula (I) is not ... (2) a substituted dihydroxyl aromatic compound, in which the two

hydroxyl groups are not adjacent to each other." The *proviso* is important because it excludes a number of compounds, *including gentisic acid*, which the Examiner submits is equally suitable and thus somehow makes Formula I obvious, as discussed below.

The Vanderheyden Reference Fails To Teach Any Compounds Of Formula I

In spite of the claim limitation and disclosure, the Examiner applies the Vanderheyden reference, which discloses radionuclides, human serum, and "antioxidants such as ascorbic acid, gentisic acid, reductic acid, derivatives thereof ... ." The Examiner has failed to show that these compounds are obvious variants of Formula I. **In fact, Formula I excludes all three of the compounds by structure or proviso.** Thus, these compounds cannot add to a *prima facie* case of obviousness. As mentioned above, the Appellant's specification also teaches that gentisic acid is excluded from the invention. *Appellant's specification* at page 29, lines 23-31.

Moreover, citation of the reference is improper, as it adds nothing to indicate obviousness of Appellant's Formula I. The Examiner states that the reference teaches that antioxidants are stabilizers, but this generalization improperly boils the invention down to a gist, namely, that the invention is adding an antioxidant to a radiopharmaceutical. This fails to give weight to all limitations of the claims, and is improper.

The Nippon Oils and Fats Reference

The Examiner then turns to the abstract of the Nippon Oils and Fats reference to supply the deficiencies of the other references. The Derwent World Patents Index abstract (attached to the back of the attached reference copy) states "[b]y combining L-ascorbic acid in gallic acid, the discolouration with iron can be prevented, and also the antioxidising

activity of gallic acid is synergically intensified. Oxidn. of the oil and fat in feed, can be prevented."

The citation of the reference is either improper in and of itself, or alternatively, it teaches away from combination with the other references.

The Nippon Oils and Fats Reference is Nonanalogous Art

Despite the number of pharmaceutical composition patents that are of record in the case, the Examiner resorts to nonanalogous art. To be analogous art, a reference must come from the same area of art or one of which a person skilled in the art reasonably would be expected to be aware. In contrast, the Nippon Oils and Fats reference relates to "[a]ntioxidant for feed use," more particularly, a combination of antioxidants which prevents oxidation "of the oil and fat in feed." Appellant's claims are directed to compositions comprising compounds of Formula I and compounds of Formula II, not compositions for preventing oxidation of oil and fat.

A person of skill in the pharmaceutical art should not be imputed to be aware of the disclosure of the Nippon Oils and Fats reference. Appellant has stated that "[u]pon information and belief, the oxidation of fats and oils in feed renders the feed less palatable to cattle, swine, and the like - thus causing reduced consumption and hence, reduced weight gain. Thus, not even a similar problem is solved." *Appellant's response* dated July 15, 2004.

The Nippon Oils and Fats Reference Teaches Away From Combination

Assuming *arguendo* that the pharmaceutical and animal feed arts are sufficiently analogous, the Nippon Oils and Fats reference would still not support a finding of obviousness. The Nippon Oils and Fats reference is limited to using ascorbic acid in gallic acid, wherein "the antioxidising activity of gallic acid is synergically intensified."

If the ascorbic acid were not removed, the reference would not meet Appellant's claim limitation for Formula I. Thus, the Examiner cites the reference as supplying gallic acid. However, ascorbic acid is not an optional component. **The synergistic result requires the presence of ascorbic acid.** Since teachings and suggestions of the Nippon Oils and Fats reference clearly requires the presence of ascorbic acid, **the reference teaches away from any modification to remove the ascorbic acid**.

Secondly, the Nippon Oils and Fats reference fails to teach the desirability of using gallic acid with radionuclides (the Vanderheyden reference also fails in this respect). The fact that something can be ingested as a feed when diluted with ascorbic acid is hardly evidence that it will function well when parenterally administered as a radiolabeled pharmaceutical agent.

The Examiner states (without support) that gallic acid and gentisic acid are equally suitable, but this is directly rebutted by the Appellant's specification, which excludes gentisic acid, but not gallic acid. The Examiner has ignored not just the teachings of the specification, but also the references. For example, the Toner reference discloses that not all antioxidants work equally well in pharmaceuticals in the Background section, which explains that **choosing the identity of the antioxidant is critical**:

> Another problem with some prior art compositions is that the chelator must be activated by a reducing agent before forming the radionuclide chelate. If the protein conjugates are to be formed prior to formation of the radionuclide chelate, then the reducing agent employed for activating the complexing agent can degrade the protein.

Thus, the references of record strongly rebut the implication that antioxidants are interchangeable. The Examiner is impermissibly using hindsight based on Appellant's disclosure to state that gallic acid would be a suitable radiopharmaceutical ingredient.

Since no permissible source suggests the desirability of combining compounds of Formula I with compounds of Formula II, a *prima facie* case of obviousness has not been

made by the Examiner. As the Examiner has not met his burden, Appellants are under no obligation to present evidence of nonobviousness.

Whether Claims 19-22, 30-33, and 35-39 are unpatentable under 35 U.S.C. §103(a) over the Rajopadhye reference in view of the Vanderheyden reference and further in view of the Nippon Oils and Fats reference.

At the time the invention of Application U.S. Serial No. 09/899,629 was made, Application U.S. Serial No. 09/899,629 and U.S. Patent No. 6,537,520 were both owned by, or subject to an obligation of assignment to, DuPont Pharmaceuticals Company. They are now commonly owned by Bristol-Myers Squibb Pharma Company. Thus, the Rajopadhye reference is not available for 35 U.S.C. §103(a) by virtue of 35 U.S.C. §103(c).

Even were this not the case, a *prima facie* case of obviousness has not been established, due to the deficiencies of the Vanderheyden and Nippon Fats and Oils references mentioned above.

Whether the Examiner has demonstrated that Claims 19-22, 30-33, and 35-39 are unpatentable under 35 U.S.C. §103(a) over the Sworin reference or the Toner reference in view of the Vanderheyden reference and further in view of the Nippon Oils and Fats reference.

No compounds of Formula I are taught or suggested by the Sworin reference or the Toner reference. In fact the Examiner is of the opinion that "[t]he primary references do not teach expressly adding stabilizers." *Office Action* dated Oct. 28, 2003. Nonetheless, the Examiner has rejected the claims, citing the Vanderheyden reference (which predates the Sworin reference and the Toner reference) as support that a stabilizer is required in those

references, despite the fact that the Vanderheyden reference also fails to teach any compounds of Formula I.

As those references all fail to teach any compounds of Formula I, the Nippon Oils and Fats reference is supplied by the Examiner. However, absent impermissible hindsight, there is no motivation to combine the Nippon Oils and Fats reference to the other references.

Assuming *arguendo* that the pharmaceutical and animal feed arts are sufficiently analogous, the Nippon Oils and Fats reference would still not support a finding of obviousness because the Nippon Oils and Fats reference is limited to using ascorbic acid in gallic acid, wherein "the antioxidising activity of gallic acid is synergically intensified." Thus, **ascorbic acid is not an optional component. The synergistic result requires the presence of ascorbic acid.** This teaches away from modification to remove the ascorbic acid. Yet to meet Appellant's Formula I, ascorbic acid would have to be removed. Since there is no suggestion to do this, the claim is not obvious, and the combination is improper.

The Nippon Oils and Fats reference fails to teach the desirability of using gallic acid with radionuclides (the Vanderheyden reference also fails in this respect). The Examiner states (without support) that gallic acid and gentisic acid are equally suitable, but this is directly rebutted by the Appellant's specification, which excludes gentisic acid, but not gallic acid.

The Examiner has ignored not just the teachings of the specification, but also the references. As shown above, the references rebut the implication that antioxidants are interchangeable. The Examiner is impermissibly using hindsight based on Appellant's disclosure to state that gallic acid would be a suitable radiopharmaceutical ingredient.

Since no permissible source suggests the desirability of combining compounds of Formula I with compounds of Formula II, a *prima facie* case of obviousness has not been

made by the Examiner. As the Examiner has not met his burden, Appellants are under no obligation to present evidence of nonobviousness.

B. ISSUES WITH RESPECT TO DEPENDENT CLAIMS 20-22, 30-33, AND 35-39

Whether the Examiner has demonstrated that Claims 19-22, 30-33, and 35-39 are unpatentable under the judicially created doctrine of obviousness-type double patenting over claims 22, and 28-30 of the Rajopadhye reference in view of the Vanderheyden reference and further in view of the Nippon Oils and Fats reference.

a. Claim 20 Not Obvious Over the Combination of References

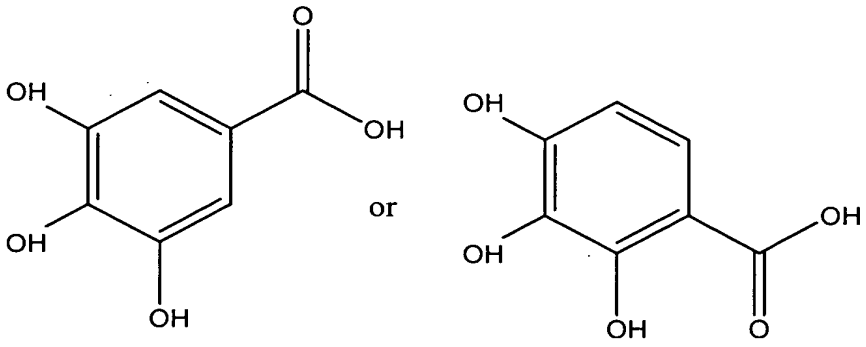
Claim 20 enjoys the benefits of independent claim 19, but with the further limitation that E^1 is OH; A^1, A^2, A^3, and A^4 are each independently C(OH) or CR^1; A^5 is C(OH); each R^1 is independently H, $C(O)R^2$, $C(O)OR^2$, $NHC(=O)NHR^2$, $NHC(=S)NHR^2$, $OC(=O)R^2$, $OC(=O)OR^2$, $S(O)_2OR^2$, $C(O)NR^3R^4$, $C(O)NR^3OR^4$, $C(O)NR^2NR^3R^4$, NR^3R^4, $NR^3C(O)R^4$, $PO(OR^3)(OR^4)$, $S(O)_2NR^3R^4$, $S(O)_2NR^2NR^3R^4$, $S(O)_2NR^3OR^4$, C_1-C_{10} alkyl substituted with 0-3 R^5,C_3-C_{10} cycloalkyl substituted with 0-3 R^5, C_2-C_{10} alkenyl substituted with 0-3 or aryl substituted with 0-5 R^5; R^2, R^3, and R^4 are each independently H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, benzyl, or phenyl; or R^3 and R^4 together form C_3-C_{10} cycloalkyl optionally interrupted with O, S, NH, S(=O), $S(O)_2$, P(=O)(OH), C(=O)NH, NHC(=O), NHC(=O)NH, or NHC(=S)NH; and each R^5 is independently H, NH_2, OH, CO_2H, $C(=O)NH_2$, PO_3H_2, SO_3H, or $S(O)_2NH_2$. The Examiner has not met his *prima facie* burden with respect to the claim. Furthermore, the references, whether taken together or separately, fail to disclose, teach, or suggest the limitation recited in the claims, and therefore the Examiner's burden is not met.

b. Claim 21 Not Obvious Over the Combination of References

Claim 21 enjoys the benefits of claim 20, but with the further limitation that A^4 is C(OH); and each R^1 is independently C(O)H, $C(O)NH_2$, $C(O)NHNH_2$, CO_2H, $NHC(=O)NH_2$, $NHC(=S)NH_2$, PO_3H_2, SO_3H, or $S(O)_2NH_2$. The Examiner has not met his *prima facie* burden with respect to the claim. Furthermore, the references, whether taken together or separately, fail to disclose, teach, or suggest the limitation recited in the claims, and therefore the Examiner's burden is not met.

c. Claim 22 Not Obvious Over the Combination of References

Claim 22 enjoys the benefits of claim 21, but with the further limitation that the compound of formula (I) is:



or a pharmaceutically acceptable salt thereof. The Examiner has not met his *prima facie* burden with respect to the claim. Furthermore, the references, whether taken together or separately, fail to disclose, teach, or suggest the limitation recited in the claims, and therefore the Examiner's burden is not met.

d. Claim 30 Not Obvious Over the Combination of References

Claim 30 enjoys the benefits of claim 19, but with the further limitation that wherein the compound of formula (I) is present at a concentration of about 0.1 mg/mL to about 20 mg/mL. The Examiner has not met his *prima facie* burden with respect to the claim.

Furthermore, the references, whether taken together or separately, fail to disclose, teach, or suggest the limitation recited in the claims, and therefore the Examiner's burden is not met.

e. Claim 31 Not Obvious Over the Combination of References

Claim 31 enjoys the benefits of claim 30, but with the further limitation that the radioisotope is present at a level of about 20 mCi to about 2000 mCi and at a concentration of greater than about 5 mCi/mL of the radiopharmaceutical composition. The Examiner has not met his *prima facie* burden with respect to the claim. Furthermore, the references, whether taken together or separately, fail to disclose, teach, or suggest the limitation recited in the claims, and therefore the Examiner's burden is not met.

f. Claim 32 Not Obvious Over the Combination of References

Claim 32 enjoys the benefits of claim 31, but with the further limitation that the radioisotope is ^{90}Y or ^{177}Lu. The Examiner has not met his *prima facie* burden with respect to the claim. Furthermore, the references, whether taken together or separately, fail to disclose, teach, or suggest the limitation recited in the claims, and therefore the Examiner's burden is not met.

g. Claim 33 Not Obvious Over the Combination of References

Claim 33 enjoys the benefits of claim 19, but with the further limitation that the biomolecule is a peptide. The Examiner has not met his *prima facie* burden with respect to the claim. Furthermore, the references, whether taken together or separately, fail to disclose, teach, or suggest the limitation recited in the claims, and therefore the Examiner's burden is not met.

h. Claim 35 Not Obvious Over the Combination of References

Claim 35 enjoys the benefits of claim 19, but with the further limitation that the biomolecule is a peptidomimetic. The Examiner has not met his *prima facie* burden with respect to the claim. Furthermore, the references, whether taken together or separately, fail to disclose, teach, or suggest the limitation recited in the claims, and therefore the Examiner's burden is not met.

i. Claim 36 Not Obvious Over the Combination of References

Claim 36 enjoys the benefits of claim 19, but with the further limitation that the biomolecule is an antibody. The Examiner has not met his *prima facie* burden with respect to the claim. Furthermore, the references, whether taken together or separately, fail to disclose, teach, or suggest the limitation recited in the claims, and therefore the Examiner's burden is not met.

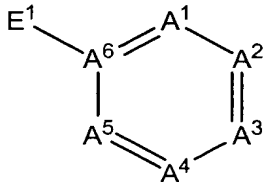
j. Claim 37 Not Obvious Over the Combination of References

Claim 37 enjoys the benefits of claim 19, but with the further limitation that the biomolecule is an antibody fragment. The Examiner has not met his *prima facie* burden with respect to the claim. Furthermore, the references, whether taken together or separately, fail to disclose, teach, or suggest the limitation recited in the claims, and therefore the Examiner's burden is not met.

k. Claim 38 Not Obvious Over the Combination of References

Claim 38 enjoys the benefits of claim 19, but with the further limitation that the composition further comprises an effective stabilizing amount of a second stabilizer selected from the group consisting of ascorbic acid, benzyl alcohol, gentisic acid, an ester of gentisic

acid, gentisyl alcohol, an ester of gentisyl alcohol, *p*-aminobenzoic acid, cystamine, cystamine, 5-amino-2-hydroxybenzoic acid, nicotinic acid, nicotinamide, propylene glycol, dextran, inositol, a compound of formula (I):



wherein, E^1 isNH_2 or OH; A^1, A^2, A^3, A^4 and A^5 are each independently N, C(OH) or CR^1; provided at least one of A^1, A^2, A^3, A^4 and A^5 is not CH; each R^1 is independently H, $C(O)R^2$, $C(O)OR^2$, $NHC(=O)NHR^2$, $NHC(=S)NHR^2$, $OC(=O)R^2$, $OC(=O)OR^2$, $S(O)_2OR^2$, $C(O)NR^3R^4$, $C(O)NR^3OR^4$, $C(O)NR^2NR^3R^4$, NR^3R^4, $NR^3C(O)R^4$, $PO(OR^3)(OR^4)$, $S(O)_2NR^3R^4$, $S(O)_2NR^2NR^3R^4$, $S(O)_2NR^3OR^4$, C_1-C_{10} alkyl substituted with 0-5 R^5, C_3-C_{10} cycloalkyl substituted with 0-5 R^5, C_2-C_{10} alkenyl substituted with 0-5 R^5, or aryl substituted with 0-5 R^5; R^2, R^3, and R^4 are each independently H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkenyl, benzyl, or phenyl; or R^3 and R^4 together form C_3-C_{10} cycloalkyl or C_3-C_{10} cycloalkenyl, optionally interrupted with O, S, NH, S(=O), $S(O)_2$, P(=O)(OH), C(=O)NH, NHC(=O), NHC(=O)NH, or NHC(=S)NH; and each R^5 is independently H, NH_2, OH, CO_2H, $C(=O)NH_2$, C(=O)NHOH, $C(=O)NHNH_2$, $NHC(=NH)NH_2$, $NHC(=O)NH_2$, $NHC(=S)NH_2$, PO_3H_2, SO_3H, or $S(O)_2NH_2$ or a pharmaceutically acceptable salt thereof. The Examiner has not met his *prima facie* burden with respect to the claim. Furthermore, the references, whether taken together or separately, fail to disclose, teach, or suggest the limitation recited in the claims, and therefore the Examiner's burden is not met.

l. Claim 39 Not Obvious Over the Combination of References

Claim 39 enjoys the benefits of claim 38, but with the further limitation that the second stabilizer is present at a concentration of about 0.1 mg/mL to about 20 mg/mL. The Examiner has not met his *prima facie* burden with respect to the claim. Furthermore, the references, whether taken together or separately, fail to disclose, teach, or suggest the limitation recited in the claims, and therefore the Examiner's burden is not met.

Whether Claims 19-22, 30-33, and 35-39 are unpatentable under 35 U.S.C. §103(a) over the Rajopadhye reference in view of the Vanderheyden reference and further in view of the Nippon Oils and Fats reference.

The Rajopadhye reference is not available for 35 U.S.C. §103(a) by virtue of 35 U.S.C. §103(c) (see above). As the dependent claims 20-22, 30-33, and 35-39 depend from and further limit claim 19, the rejection cannot be applied against these claims either.

Whether the Examiner has demonstrated that Claims 19-22, 30-33, and 35-39 are unpatentable under 35 U.S.C. §103(a) over the Sworin reference or the Toner reference in view of the Vanderheyden reference and further in view of the Nippon Oils and Fats reference.

a. Claim 20 Not Obvious Over the Combination of References

Claim 20 enjoys the benefits of independent claim 19, but with the further limitation that E^1 is OH; A^1, A^2, A^3, and A^4 are each independently C(OH) or CR^1; A^5 is C(OH); each R^1 is independently H, $C(O)R^2$, $C(O)OR^2$, $NHC(=O)NHR^2$, $NHC(=S)NHR^2$, $OC(=O)R^2$, $OC(=O)OR^2$, $S(O)_2OR^2$, $C(O)NR^3R^4$, $C(O)NR^3OR^4$, $C(O)NR^2NR^3R^4$, NR^3R^4, $NR^3C(O)R^4$, $PO(OR^3)(OR^4)$, $S(O)_2NR^3R^4$, $S(O)_2NR^2NR^3R^4$, $S(O)_2NR^3OR^4$, C_1-C_{10} alkyl substituted with 0-3 R^5, C_3-C_{10} cycloalkyl substituted with 0-3 R^5, C_2-C_{10} alkenyl substituted with 0-3 or aryl

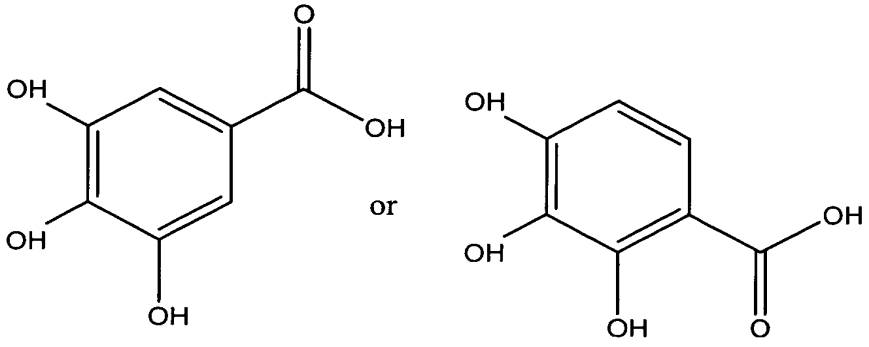
substituted with 0-5 R^5; R^2, R^3, and R^4 are each independently H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, benzyl, or phenyl; or R^3 and R^4 together form C_3-C_{10} cycloalkyl optionally interrupted with O, S, NH, S(=O), $S(O)_2$, P(=O)(OH), C(=O)NH, NHC(=O), NHC(=O)NH, or NHC(=S)NH; and each R^5 is independently H, NH_2, OH, CO_2H, $C(=O)NH_2$, PO_3H_2, SO_3H, or $S(O)_2NH_2$. The Examiner has not met his *prima facie* burden with respect to the claim. Furthermore, the references, whether taken together or separately, fail to disclose, teach, or suggest the limitation recited in the claims, and therefore the Examiner's burden is not met.

b. Claim 21 Not Obvious Over the Combination of References

Claim 21 enjoys the benefits of claim 20, but with the further limitation that A^4 is C(OH); and each R^1 is independently C(O)H, $C(O)NH_2$, $C(O)NHNH_2$, CO_2H, $NHC(=O)NH_2$, $NHC(=S)NH_2$, PO_3H_2, SO_3H, or $S(O)_2NH_2$. The Examiner has not met his *prima facie* burden with respect to the claim. Furthermore, the references, whether taken together or separately, fail to disclose, teach, or suggest the limitation recited in the claims, and therefore the Examiner's burden is not met.

c. Claim 22 Not Obvious Over the Combination of References

Claim 22 enjoys the benefits of claim 21, but with the further limitation that the compound of formula (I) is:



or a pharmaceutically acceptable salt thereof. The Examiner has not met his *prima facie* burden with respect to the claim. Furthermore, the references, whether taken together or separately, fail to disclose, teach, or suggest the limitation recited in the claims, and therefore the Examiner's burden is not met.

d. Claim 30 Not Obvious Over the Combination of References

Claim 30 enjoys the benefits of claim 19, but with the further limitation that wherein the compound of formula (I) is present at a concentration of about 0.1 mg/mL to about 20 mg/mL. The Examiner has not met his *prima facie* burden with respect to the claim. Furthermore, the references, whether taken together or separately, fail to disclose, teach, or suggest the limitation recited in the claims, and therefore the Examiner's burden is not met.

e. Claim 31 Not Obvious Over the Combination of References

Claim 31 enjoys the benefits of claim 30, but with the further limitation that the radioisotope is present at a level of about 20 mCi to about 2000 mCi and at a concentration of greater than about 5 mCi/mL of the radiopharmaceutical composition. The Examiner has not met his *prima facie* burden with respect to the claim. Furthermore, the references, whether taken together or separately, fail to disclose, teach, or suggest the limitation recited in the claims, and therefore the Examiner's burden is not met.

f. Claim 32 Not Obvious Over the Combination of References

Claim 32 enjoys the benefits of claim 31, but with the further limitation that the radioisotope is ^{90}Y or ^{177}Lu. The Examiner has not met his *prima facie* burden with respect to the claim. Furthermore, the references, whether taken together or separately, fail to

disclose, teach, or suggest the limitation recited in the claims, and therefore the Examiner's burden is not met.

g. Claim 33 Not Obvious Over the Combination of References

Claim 33 enjoys the benefits of claim 19, but with the further limitation that the biomolecule is a peptide. The Examiner has not met his *prima facie* burden with respect to the claim. Furthermore, the references, whether taken together or separately, fail to disclose, teach, or suggest the limitation recited in the claims, and therefore the Examiner's burden is not met.

h. Claim 35 Not Obvious Over the Combination of References

Claim 35 enjoys the benefits of claim 19, but with the further limitation that the biomolecule is a peptidomimetic. The Examiner has not met his *prima facie* burden with respect to the claim. Furthermore, the references, whether taken together or separately, fail to disclose, teach, or suggest the limitation recited in the claims, and therefore the Examiner's burden is not met.

i. Claim 36 Not Obvious Over the Combination of References

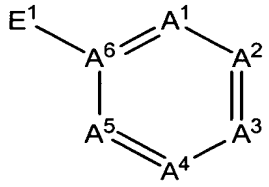
Claim 36 enjoys the benefits of claim 19, but with the further limitation that the biomolecule is an antibody. The Examiner has not met his *prima facie* burden with respect to the claim. Furthermore, the references, whether taken together or separately, fail to disclose, teach, or suggest the limitation recited in the claims, and therefore the Examiner's burden is not met.

j. Claim 37 Not Obvious Over the Combination of References

Claim 37 enjoys the benefits of claim 19, but with the further limitation that the biomolecule is an antibody fragment. The Examiner has not met his *prima facie* burden with respect to the claim. Furthermore, the references, whether taken together or separately, fail to disclose, teach, or suggest the limitation recited in the claims, and therefore the Examiner's burden is not met.

k. Claim 38 Not Obvious Over the Combination of References

Claim 38 enjoys the benefits of claim 19, but with the further limitation that the composition further comprises an effective stabilizing amount of a second stabilizer selected from the group consisting of ascorbic acid, benzyl alcohol, gentisic acid, an ester of gentisic acid, gentisyl alcohol, an ester of gentisyl alcohol, *p*-aminobenzoic acid, cystamine, cystamine, 5-amino-2-hydroxybenzoic acid, nicotinic acid, nicotinamide, propylene glycol, dextran, inositol, a compound of formula (I):



wherein, E^1 isNH_2 or OH; A^1, A^2, A^3, A^4 and A^5 are each independently N, C(OH) or CR^1; provided at least one of A^1, A^2, A^3, A^4 and A^5 is not CH; each R^1 is independently H, $C(O)R^2$, $C(O)OR^2$, $NHC(=O)NHR^2$, $NHC(=S)NHR^2$, $OC(=O)R^2$, $OC(=O)OR^2$, $S(O)_2OR^2$, $C(O)NR^3R^4$, $C(O)NR^3OR^4$, $C(O)NR^2NR^3R^4$, NR^3R^4, $NR^3C(O)R^4$, $PO(OR^3)(OR^4)$, $S(O)_2NR^3R^4$, $S(O)_2NR^2NR^3R^4$, $S(O)_2NR^3OR^4$, C_1-C_{10} alkyl substituted with 0-5 R^5, C_3-C_{10} cycloalkyl substituted with 0-5 R^5, C_2-C_{10} alkenyl substituted with 0-5 R^5, or aryl substituted with 0-5 R^5; R^2, R^3, and R^4 are each independently H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkenyl, benzyl, or phenyl; or R^3 and R^4 together form C_3-C_{10} cycloalkyl or C_3-C_{10}

cycloalkenyl, optionally interrupted with O, S, NH, S(=O), $S(O)_2$, P(=O)(OH), C(=O)NH, NHC(=O), NHC(=O)NH, or NHC(=S)NH; and each R^5 is independently H, NH_2, OH, CO_2H, $C(=O)NH_2$, C(=O)NHOH, $C(=O)NHNH_2$, $NHC(=NH)NH_2$, $NHC(=O)NH_2$, $NHC(=S)NH_2$, PO_3H_2, SO_3H, or $S(O)_2NH_2$ or a pharmaceutically acceptable salt thereof. The Examiner has not met his *prima facie* burden with respect to the claim. Furthermore, the references, whether taken together or separately, fail to disclose, teach, or suggest the limitation recited in the claims, and therefore the Examiner's burden is not met.

l. Claim 39 Not Obvious Over the Combination of References

Claim 39 enjoys the benefits of claim 38, but with the further limitation that the second stabilizer is present at a concentration of about 0.1 mg/mL to about 20 mg/mL. The Examiner has not met his *prima facie* burden with respect to the claim. Furthermore, the references, whether taken together or separately, fail to disclose, teach, or suggest the limitation recited in the claims, and therefore the Examiner's burden is not met.

The claims are separately patentable.

The foregoing arguments have demonstrated that the claims are separately patentable, and thus do not stand or fall together.

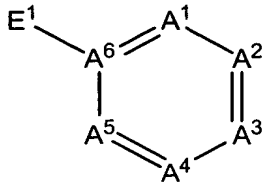
9. APPENDIX

1. (Withdrawn) A pharmaceutical composition comprising:

(1.) a radiolabeled pharmaceutical agent of the formula (II)

$$RI\text{-}Ch\text{-}L_n\text{-}(BM)_x \qquad (II);$$ and

(2.) an effective stabilizing amount of a compound of formula (I):



wherein

RI is ^{99m}Tc, ^{131}I, ^{125}I, ^{123}I, ^{117m}Sn, ^{111}In, ^{97}Ru, ^{203}Pb, ^{67}Ga, ^{68}Ga, ^{89}Zr, ^{90}Y, ^{177}Lu, ^{149}Pm, ^{153}Sm, ^{166}Ho, ^{131}I, ^{32}P, ^{211}At, ^{47}Sc, ^{109}Pd, ^{105}Rh, ^{186}Re, ^{188}Re, ^{60}Cu, ^{62}Cu, ^{64}Cu or ^{67}Cu;

C_h is a metal chelator or is a direct linkage;

L_n is a linking group or is a direct linkage;

each BM is independently a peptidomimetic or a non-peptide;

x is 1 to about 10;

E^1 is NH_2 or OH;

A^1, A^2, A^3, A^4 and A^5 are each independently N, C(OH) or CR^1; provided at least one of A^1, A^2, A^3, A^4 and A^5 is not CH;

each R^1 is independently H, $C(O)R^2$, $C(O)OR^2$, $NHC(=O)NHR^2$, $NHC(=S)NHR^2$, $OC(=O)R^2$, $OC(=O)OR^2$, $S(O)_2OR^2$, $C(O)NR^3R^4$, $C(O)NR^3OR^4$, $C(O)NR^2NR^3R^4$, NR^3R^4, $NR^3C(O)R^4$, $PO(OR^3)(OR^4)$, $S(O)_2NR^3R^4$, $S(O)_2NR^2NR^3R^4$, $S(O)_2NR^3OR^4$, C_1-C_{10} alkyl substituted with 0-5 R^5, C_3-C_{10} cycloalkyl substituted with 0-5 R^5, C_2-C_{10} alkenyl substituted with 0-5 R^5, or aryl substituted with 0-5 R^5;

R^2, R^3, and R^4 are each independently H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkenyl, benzyl, or phenyl; or R^3 and R^4 together form C_3-C_{10} cycloalkyl or C_3-C_{10} cycloalkenyl, optionally interrupted with O, S, NH, S(=O), $S(O)_2$, P(=O)(OH), C(=O)NH, NHC(=O), NHC(=O)NH, or NHC(=S)NH; and

each R^5 is independently H, NH_2, OH, CO_2H, $C(=O)NH_2$, C(=O)NHOH, $C(=O)NHNH_2$, $NHC(=NH)NH_2$, $NHC(=O)NH_2$, $NHC(=S)NH_2$, PO_3H_2, SO_3H,br $S(O)_2NH_2$;

or a pharmaceutically acceptable salt thereof.

2. (Withdrawn) The composition of claim 1 wherein

E_1 is OH;

A^1, A^2, A^3, and A^4 are each independently C(OH) or CR^1;

A^5 is C(OH);

each R^1 is independently H, $C(O)R^2$, $C(O)OR^2$, $NHC(=O)NHR^2$, $NHC(=S)NHR^2$, $OC(=O)R^2$, $OC(=O)OR^2$, $S(O)_2OR^2$, $C(O)NR^3R^4$, $C(O)NR^3OR^4$, $C(O)NR^2NR^3R^4$, NR^3R^4,

$NR^3C(O)R^4$, $PO(OR^3)(OR^4)$, $S(O)_2NR^3R^4$, $S(O)_2NR^2NR^3R^4$, $S(O)_2NR^3OR^4$, C_1-C_{10} alkyl substituted with 0-3 R^5, C_3-C_{10} cycloalkyl substituted with 0-3 R^5, C_2-C_{10} alkenyl substituted with 0-3 R^5, or aryl substituted with 0-5 R^5;

R^2, R^3, and R^4 are each independently H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, benzyl, or phenyl; or R^3 and R^4 together form C_3-C_{10} cycloalkyl optionally interrupted with O, S, NH, S(=O), $S(O)_2$, P(=O)(OH), C(=O)NH, NHC(=O), NHC(=O)NH, or NHC(=S)NH; and

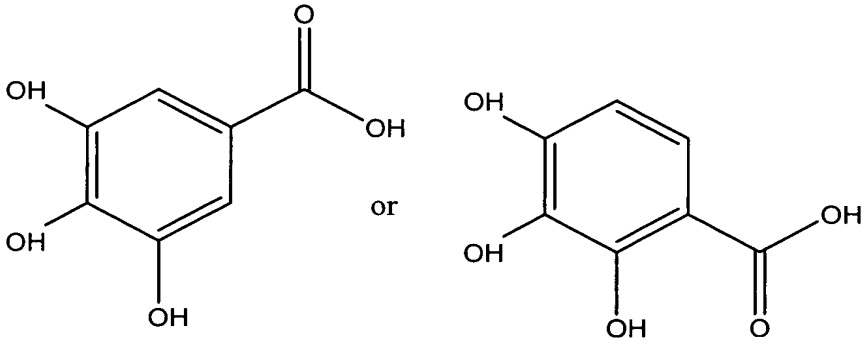
each R^5 is independently H, NH_2, OH, CO_2H, $C(=O)NH_2$, PO_3H_2, SO_3H, or $S(O)_2NH_2$.

3. (Withdrawn) The composition of claim 2 wherein,

A^4 is C(OH); and

each R^1 is independently C(O)H, $C(O)NH_2$, $C(O)NHNH_2$, CO_2H, $NHC(=O)NH_2$, $NHC(=S)NH_2$, PO_3H_2, SO_3H, or $S(O)_2NH_2$.

4. (Withdrawn) The composition of claim 3 wherein the compound of formula (I) is:



or a pharmaceutically acceptable salt thereof.

5. (Withdrawn) The composition of claim 1 wherein

E^1 is NH_2;

A^1, A^2, A^3, and A^4 are each independently C(OH) or CR^1;

A^5 is C(OH);

each R^1 is independently H, $C(O)R^2$, $C(O)OR^2$, $NHC(=O)NHR^2$, $NHC(=S)NHR^2$, $OC(=O)R^2$, $OC(=O)OR^2$, $S(O)_2OR^2$, $C(O)NR^3R^4$, $C(O)NR^3OR^4$, $C(O)NR^2NR^3R^4$, NR^3R^4, $NR^3C(O)R^4$, $PO(OR^3)(OR^4)$, $S(O)_2NR^3R^4$, $S(O)_2NR^2NR^3R^4$, $S(O)_2NR^3OR^4$, C_1-C_{10} alkyl substituted with 0-3 R^5, C_3-C_{10} cycloalkyl substituted with 0-3 R^5, C_2-C_{10} alkenyl substituted with 0-3 R^5, or aryl substituted with 0-5 R^5;

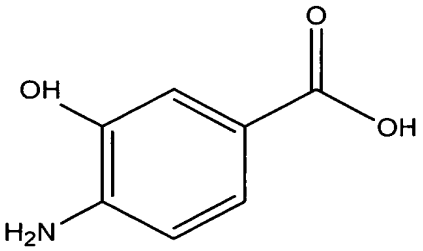
R^2, R^3, and R^4 are each independently H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, benzyl, or phenyl; or R^3 and R^4 together form C_3-C_{10} cycloalkyl optionally interrupted with O, S, NH, S(=O), $S(O)_2$, P(=O)(OH), C(=O)NH, NHC(=O), NHC(=O)NH, or NHC(=S)NH; and

each R^5 is independently H, NH_2, OH, CO_2H, $C(=O)NH_2$, PO_3H_2, SO_3H, or $S(O)_2NH_2$.

6. (Withdrawn) The composition of claim 5 wherein

each R^1 is independently C(O)H, $C(O)NH_2$, $C(O)NHNH_2$, CO_2H, $NHC(=O)NH_2$, $NHC(=S)NH_2$, PO_3H_2, SO_3H, or $S(O)_2NH_2$.

7. (Withdrawn) The composition of claim 6 wherein compound of the formula (I) is a compound of the formula:



or a pharmaceutically acceptable salt thereof.

8. (Withdrawn) The composition of claim 1 wherein

A^1, A^2, A^3, A^4, and A^5 are each independently N, C(OH) or CR^1; provided that A^5 is not C(OH);

each R^1 is independently H, $C(O)R^2$, $C(O)OR^2$, $NHC(=O)NHR^2$, $NHC(=S)NHR^2$, $OC(=O)R^2$, $OC(=O)OR^2$, $S(O)_2OR^2$, $C(O)NR^3R^4$, $C(O)NR^3OR^4$, $C(O)NR^2NR^3R^4$, NR^3R^4, $NR^3C(O)R^4$, $PO(OR^3)(OR^4)$, $S(O)_2NR^3R^4$, $S(O)_2NR^2NR^3R^4$, $S(O)_2NR^3OR^4$, C_1-C_{10} alkyl substituted with 0-5 R^5, C_3-C_{10} cycloalkyl substituted with 0-5 R^5, C_2-C_{10} alkenyl substituted with 0-5 R^5 or aryl substituted with 0-5 R^5;

R^2, R^3, and R^4 are each independently H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C,-C_6 alkenyl, benzyl, or phenyl; or R^3 and R^4 together form C_3-C_{10} cycloalkyl or C_3-C_{10} cycloalkenyl optionally interrupted with O, S, NH, S(=O), $S(O)_2$, P(=O)(OH), C(=O)NH, NHC(=O), NHC(=O)NH, or NHC(=S)NH; and

each R^5 is independently H, NH_2, OH, CO_2H, $C(=O)NH_2$, C(=O)NHOH, $C(=O)NHNH_2$, $NHC(=NH)NH_2$, $NHC(=O)NH_2$, $NHC(=S)NH_2$, PO_3H_2, SO_3H, or $S(O)_2NH_2$.

9. (Withdrawn) The composition of claim 8 wherein

A^1, A^2, A^3, A^4, and A^5 are each independently CR^1;

each R^1 is independently H, $C(O)R^2$, $C(O)OR^2$, $NHC(=O)NHR^2$, $NHC(=S)NHR^2$, $OC(=O)R^2$, $OC(=O)OR^2$, $S(O)_2OR^2$, $C(O)NR^3R^4$, $C(O)NR^3OR^4$, $C(O)NR^2NR^3R^4$, NR^3R^4, $NR^3C(O)R^4$, $PO(OR^3)(OR^4)$, $S(O)_2NR^3R^4$, $S(O)_2NR^2NR^3R^4$, $S(O)_2NR^3OR^4$, C_1-C_{10} alkyl substituted with 0-3 R^5, C_3-C_{10} cycloalkyl substituted with 0-3 R^5, C_2-C_{10} alkenyl substituted with 0-3 R^5, or aryl substituted with 0-5 R^5;

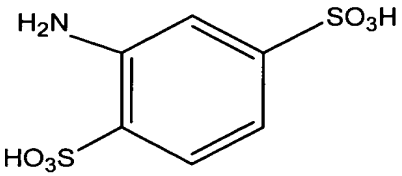
R^2, R^3, and R^4 are each independently H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, benzyl, or phenyl; or R^3 and R^4 together form C_3-C_{10} cycloalkyl optionally interrupted with O, S, NH; S(=O), $S(O)_2$, P(=O)(OH), C(=O)NH, NHC(=O), NHC(=O)NH, or NHC(=S)NH; and

each R^5 is independently H, NH_2, OH, CO_2H, $C(=O)NH_2$, PO_3H_2, SO_3H, or $S(O)_2NH_2$.

10. (Withdrawn) The composition of claim 9 wherein

each R^1 is independently C(O)H, $C(O)NH_2$, $C(O)NHNH_2$, CO_2H, $NHC(=O)NH_2$, $NHC(=S)NH_2$, PO_3H_2, SO_3H, or $S(O)_2NH_2$.

11. (Withdrawn) The composition of claim 10 wherein the compound of formula (I) is a compound of the formula:



or a pharmaceutically acceptable salt thereof.

12. (Withdrawn) The composition of claim 1 wherein the compound of formula (I) is present at a concentration of about 0.1 mg/mL to about 20 mg/mL.

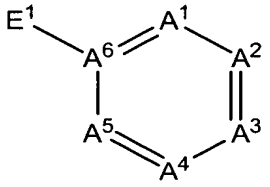
13. (Withdrawn) The composition of claim 12 wherein the radioisotope is present at a level of about 20 mCi to about 2000 mCi and is present at a concentration of greater than about 5 mCi/mL of the radiopharmaceutical composition.

14. (Withdrawn) The composition of claim 13 wherein the radioisotope is ^{90}Y or ^{177}Lu.

15. (Withdrawn) The composition of claim 1 wherein the biomolecule is a peptidomimetic.

16. (Withdrawn) The composition of claim 1 wherein the biomolecule is a non-peptide.

17. (Withdrawn) The composition of claim 1 further comprising an effective stabilizing amount of a second stabilizer selected from the group consisting of ascorbic acid, benzyl alcohol, gentisic acid, an ester of gentisic acid, gentisyl alcohol, an ester of gentisyl alcohol, *p*-aminobenzoic acid, cystamine, cystamine, 5-amino-2-hydroxybenzoic acid, nicotinic acid, nicotinamide, propylene glycol, dextran, inositol, a compound of formula (I):



wherein,

E^1 is NH_2 or OH;

A^1, A^2, A^3, A^4 and A^5 are each independently N, C(OH) or CR^1;

provided at least one of A^1, A^2, A^3, A^4 and A^5 is not CH;

each R^1 is independently H, $C(O)R^2$, $C(O)OR^2$, $NHC(=O)NHR^2$, $NHC(=S)NHR^2$, $OC(=O)R^2$, $OC(=O)OR^2$, $S(O)_2OR^2$, $C(O)NR^3R^4$, $C(O)NR^3OR^4$, $C(O)NR^2NR^3R^4$, NR^3R^4, $NR^3C(O)R^4$, $PO(OR^3)(OR^4)$, $S(O)_2NR^3R^4$, $S(O)_2NR^2NR^3R^4$, $S(O)_2NR^3OR^4$, C^1-C^{10} alkyl substituted with 0-5 R^5, C_3-C_{10} cycloalkyl substituted with 0-5 R^5, C_2-C_{10} alkenyl substituted with 0-5 R^5, or aryl substituted with 0-5 R^5;

R^2, R^3, and R^4 are each independently H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkenyl, benzyl, or phenyl; or R^3 and R^4 together form C_3-C_{10} cycloalkyl or C_3-C_{10} cycloalkenyl, optionally interrupted with O, S, NH, S(=O), $S(O)_2$, P(=O)(OH), C(=O)NH, NHC(=O), NHC(=O)NH, or NHC(=S)NH; and

each R^5 is independently H, NH_2, OH, CO_2H, $C(=O)NH_2$, C(=O)NHOH, $C(=O)NHNH_2$, $NHC(=NH)NH_2$, $NHC(=O)NH_2$, $NHC(=S)NH_2$, PO_3H_2, SO_3H, or $S(O)_2NH_2$

or a pharmaceutically acceptable salt thereof.

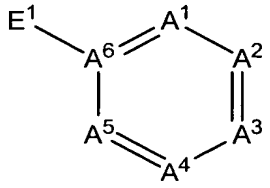
18. (Withdrawn) The composition of claim 17 wherein the second stabilizer is present at a concentration of about 0.1 mg/mL to about 20 mg/mL.

19. (Rejected; On Appeal) A pharmaceutical composition comprising:

(1.) a radiolabeled pharmaceutical agent of the formula (II)

$$RI\text{-}Ch\text{-}L_n\text{-}(BM)_x \qquad (II);$$ and

(2.) an effective stabilizing amount of a compound of formula (I):



wherein

RI is ^{99m}Tc, ^{131}I, ^{125}I, ^{123}I, ^{117m}Sn, ^{111}In, ^{97}Ru, ^{203}Pb, ^{67}Ga, ^{68}Ga, ^{89}Zr, ^{90}Y, ^{177}Lu, ^{149}Pm, ^{153}Sm, ^{166}Ho, ^{131}I, ^{32}P, ^{211}At, ^{47}Sc, ^{109}Pd, ^{105}Rh, ^{186}Re, ^{188}Re, ^{60}Cu, ^{62}Cu, ^{64}Cu, ^{67}Cu;

C_h is a metal chelator or is a direct linkage;

L_n is a linking group or is a direct linkage;

each BM is independently an antibody, an antibody fragment, a peptide, a peptidomimetic, or a non-peptide;

x is 1 to about 10;

E^1 is NH_2 or OH;

A^1, A^2, A^3, A^4 and A^5 are each independently N, C(OH) or CR^1;

provided at least one of A^1, A^2, A^3, A^4 and A^5 is not CH;

each R^1 is independently H, $C(O)R^2$, $C(O)OR^2$, $NHC(=O)NHR^2$, $NHC(=S)NHR^2$, $OC(=O)R^2$, $OC(=O)OR^2$, $S(O)_2OR^2$, $C(O)NR^3R^4$, $C(O)NR^3OR^4$, $C(O)NR^2NR^3R^4$, NR^3R^4, $NR^3C(O)R^4$, $PO(OR^3)(OR^4)$, $S(O)_2NR^3R^4$, $S(O)_2NR^2NR^3R^4$, $S(O)_2NR^3OR^4$, C_1-C_{10} alkyl substituted with 0-5 R^5, C_3-C_{10} cycloalkyl substituted with 0-5 R^5, C_2-C_{10} alkenyl substituted with 0-5 R^5, or aryl substituted with 0-5 R^5;

R^2, R^3, and R^4 are each independently H, C_1-C_6 aikyl, C_3-C_6 cycloalkyl, C_1-C_6 alkenyl, benzyl, or phenyl; or R^3 and R^4 together form C_3-C_{10} cycloalkyl or C_3-C_{10} cycloalkenyl, optionally interrupted with O, S, NH, S(=O), $S(O)_2$, P(=O)(OH), C(=O)NH, NHC(=O), NHC(=O)NH, or NHC(=S)NH; and

each R^5 is independently H, NH_2, OH, CO_2H, $C(=O)NH_2$, C(=O)NHOH, $C(=O)NHNH_2$, $NHC(=NH)NH_2$, $NHC(=O)NH_2$, $NHC(=S)NH_2$, PO_3H_2, SO_3H, or $S(O)_2NH_2$;

or a pharmaceutically acceptable salt thereof;

provided the compound of formula (I) is not (1) a substituted monohydroxyl aromatic compound; (2) a substituted dihydroxyl aromatic compound, in which the two hydroxyl groups are not adjacent to each other; (3) a substituted monohydroxyl-monoamino aromatic compound, in which the hydroxyl group and amino group are not adjacent to each other; or (4) an ortho, meta, or para aminobenzioc acid.

20. (Rejected; On Appeal) The composition of claim 19 wherein

E^1 is OH;

A^1, A^2, A^3, and A^4 are each independently C(OH) or CR^1;

A^5 is C(OH);

each R^1 is independently H, $C(O)R^2$, $C(O)OR^2$, $NHC(=O)NHR^2$, $NHC(=S)NHR^2$, $OC(=O)R^2$, $OC(=O)OR^2$, $S(O)_2OR^2$, $C(O)NR^3R^4$, $C(O)NR^3OR^4$, $C(O)NR^2NR^3R^4$, NR^3R^4, $NR^3C(O)R^4$, $PO(OR^3)(OR^4)$, $S(O)_2NR^3R^4$, $S(O)_2NR^2NR^3R^4$, $S(O)_2NR^3OR^4$, C_1-C_{10} alkyl substituted with 0-3 R^5,C_3-C_{10} cycloalkyl substituted with 0-3 R^5, C_2-C_{10} alkenyl substituted with 0-3 or aryl substituted with 0-5 R^5;

R^2, R^3, and R^4 are each independently H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, benzyl, or phenyl; or R^3 and R^4 together form C_3-C_{10} cycloalkyl optionally interrupted with O, S, NH, S(=O), $S(O)_2$, P(=O)(OH), C(=O)NH, NHC(=O), NHC(=O)NH, or NHC(=S)NH; and

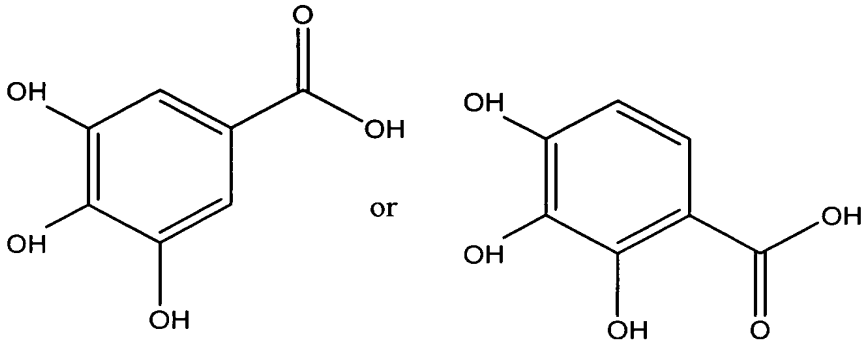
each R^5 is independently H, NH_2, OH, CO_2H, $C(=O)NH_2$, PO_3H_2, SO_3H, or $S(O)_2NH_2$.

21. (Rejected; On Appeal) The composition of claim 20 wherein,

A^4 is C(OH); and

each R^1 is independently C(O)H, $C(O)NH_2$, $C(O)NHNH_2$, CO_2H, $NHC(=O)NH_2$, $NHC(=S)NH_2$, PO_3H_2, SO_3H, or $S(O)_2NH_2$.

22. (Rejected; On Appeal) The composition of claim 21 wherein the compound of formula (I) is:



or a pharmaceutically acceptable salt thereof.

23. (Withdrawn) The composition of claim 19 wherein

E^1 is NH_2;

A^1, A^2, A^3, and A^4 are each independently C(OH) or CR^1;

A^5 is C(OH);

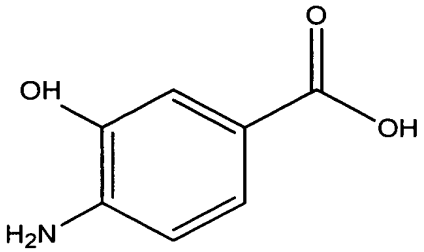
each R^1 is independently H, $C(O)R^2$, $C(O)OR^2$, $NHC(=O)NHR^2$, $NHC(=S)NHR^2$, $OC(=O)R^2$, $OC(=O)OR^2$, $S(O)_2OR^2$, $C(O)NR^3R^4$, $C(O)NR^3OR^4$, $C(O)NR^2NR^3R^4$, NR^3R^4, $NR^3C(O)R^4$, $PO(OR^3)(OR^4)$, $S(O)_2NR^3R^4$, $S(O)_2NR^2NR^3R^4$, $S(O)_2NR^3OR^4$, C_1–C_{10} alkyl substituted with 0-3 R^5, C_3-C_{10} cycloalkyl substituted with 0-3 R^5, C_2-C_{10} alkenyl substituted with 0-3 R^5, or aryl substituted with 0-5 R^5;

R^2, R^3, and R^4 are each independently H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, benzyl, or phenyl; or R^3 and R^4 together form C_3-C_{10} cycloalkyl optionally interrupted with O, S, NH, S(=O), $S(O)_2$, P(=O)(OH), C(=O)NH, NHC(=O), NHC(=O)NH, or NHC(=S)NH; and

each R^5 is independently H, NH_2, OH, CO_2H, $C(=O)NH_2$, PO_3H_2, SO_3H, or $S(O)_2NH_2$.

24. (Withdrawn) The composition of claim 23 wherein each R^1 is independently C(O)H, $C(O)NH_2$, $C(O)NHNH_2$, CO_2H, $NHC(=O)NH_2$, $NHC(=S)NH_2$, PO_3H_2, SO_3H, or $S(O)_2NH_2$.

25. (Withdrawn) The composition of claim 24 wherein compound of the formula (I) is a compound of the formula:



or a pharmaceutically acceptable salt thereof.

26. (Withdrawn) The composition of claim 19 wherein

A^1, A^2, A^3, A^4, and A^5 are each independently N, C(OH) or CR^1; provided that A^5 is not C(OH);

each R^1 is independently H, $C(O)R^2$, $C(O)OR^2$, $NHC(=O)NHR^2$, $NHC(=S)NHR^2$, $OC(=O)R^2$, $OC(=O)OR^2$, $S(O)_2OR^2$, $C(O)NR^3R^4$, $C(O)NR^3OR^4$, $C(O)NR^2NR^3R^4$, NR^3R^4, $NR^3C(O)R^4$, $PO(OR^3)(OR^4)$, $S(O)_2NR^3R^4$, $S(O)_2NR^2NR^3R^4$, $S(O)_2NR^3OR^4$, C_1-$C_{,0}$ alkyl substituted with 0-5 R^5, C_3-C_{10} cycloalkyl substituted with 0-5 R^5, C_2-C_{10} alkenyl substituted with 0-5 R^5, or aryl substituted with 0-5 R^5;

R^2, R^3, and R^4 are each independently H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, $C_{,}$-C_6 alkenyl, benzyl, or phenyl; or R^3 and R^4 together form C_3-C_{10} cycloalkyl or C_3-C_{10} cycloalkenyl optionally interrupted with O, S, NH, S(=O), $S(O)_2$, P(=O)(OH), C(=O)NH, NHC(=O), NHC(=O)NH, or NHC(=S)NH; and

each R^5 is independently H, NH_2, OH, CO_2H, $C(=O)NH_2$, C(=O)NHOH, $C(=O)NHNH_2$, $NHC(=NH)NH_2$, $NHC(=O)NH_2$, $NHC(=S)NH_2$, PO_3H_2, SO_3H, or $S(O)_2NH_2$.

27. (Withdrawn) The composition of claim 26 wherein

A^1, A^2, A^3, A^4, and A^5 are each independently CR^1

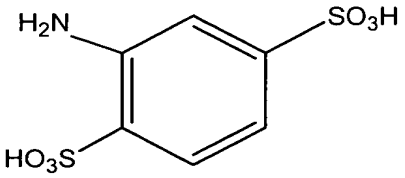
each R^1 is independently H, $C(O)R^2$, $C(O)OR^2$, $NHC(=O)NHIR^2$, $NHC(=S)NHR^2$, $OC(=O)R^2$, $OC(=O)OR^2$, $S(O)_2OR^2$, $C(O)NR^3R^4$, $C(O)NR^3OR^4$, $C(O)NR^2NR^3R^4$, NR^3R^4, $NR^3C(O)R^4$, $PO(OR^3)(OR^4)$, $S(O)_2NR^3R^4$, $S(O)_2NR^2NR^3R^4$, $S(O)_2NR^3OR^4$, C_1-C_{10} alkyl substituted with 0-3 R^5, C_3-C_{10} cycloalkyl substituted with 0-3 R^5, C_2-C_{10} alkenyl substituted with 0-3 R^5, or aryl substituted with 0-5 R^5

R^2, R^3, and R^4 are each independently H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, benzyl, or phenyl; or R^3 and R^4 together form C_3-C_{10} cycloalkyl optionally interrupted with O, S, NH, S(=O), $S(O)_2$, P(=O)(OH), C(=O)NH, NHC(=O), NHC(=O)NH, or NHC(S)NH; and

each R^5 is independently H, NH_2, OH, CO_2H, $C(=O)NH_2$, PO_3H_2, SO_3H, or $S(O)_2NH_2$.

28. (Withdrawn) The composition of claim 27 wherein
each R^1 is independently C(O)H, $C(O)NH_2$, $C(O)NHNH_2$, CO_2H, $NHC(=O)NH_2$, $NHC(=S)NH_2$, PO_3H_2, SO_3H, or $S(O)_2NH_2$.

29. (Withdrawn) The composition of claim 28 wherein the compound of formula (I) is a compound of the formula:



or a pharmaceutically acceptable salt thereof.

30. (Rejected; On Appeal) The composition of claim 19 wherein the compound of formula (I) is present at a concentration of about 0.1 mg/mL to about 20 mg/mL.

31. (Rejected; On Appeal) The composition of claim 30 wherein the radioisotope is present at a level of about 20 mCi to about 2000 mCi and at a concentration of greater than about 5 mCi/mL of the radiopharmaceutical composition.

32. (Rejected; On Appeal) The composition of claim 31 wherein the radioisotope is ^{90}Y or ^{177}Lu.

33. (Rejected; On Appeal) The composition of claim 19 wherein the biomolecule is a peptide.

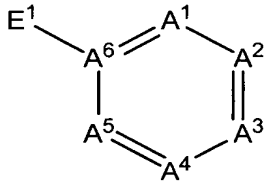
34. (Withdrawn) The composition of claim 19 wherein the biomolecule is a non-peptide.

35. (Rejected; On Appeal) The composition of claim 19 wherein the biomolecule is a peptidomimetic.

36. (Rejected; On Appeal) The composition of claim 19 wherein the biomolecule is an antibody.

37. (Rejected; On Appeal) The composition of claim 19 wherein the biomolecule is an antibody fragment.

38. (Rejected; On Appeal) The composition of claim 19 further comprising an effective stabilizing amount of a second stabilizer selected from the group consisting of ascorbic acid, benzyl alcohol, gentisic acid, an ester of gentisic acid, gentisyl alcohol, an ester of gentisyl alcohol, *p*-aminobenzoic acid, cystamine, cystamine, 5-amino-2-hydroxybenzoic acid, nicotinic acid, nicotinamide, propylene glycol, dextran, inositol, a compound of formula (I):



wherein,

E^1 is NH_2 or OH;

A^1, A^2, A^3, A^4 and A^5 are each independently N, C(OH) or CR^1; provided at least one of A^1, A^2, A^3, A^4 and A^5 is not CH;

each R^1 is independently H, $C(O)R^2$, $C(O)OR^2$, $NHC(=O)NHR^2$, $NHC(=S)NHR^2$, $OC(=O)R^2$, $OC(=O)OR^2$, $S(O)_2OR^2$, $C(O)NR^3R^4$, $C(O)NR^3OR^4$, $C(O)NR^2NR^3R^4$, NR^3R^4, $NR^3C(O)R^4$, $PO(OR^3)(OR^4)$, $S(O)_2NR^3R^4$, $S(O)_2NR^2NR^3R^4$, $S(O)_2NR^3OR^4$, C_1-C_{10} alkyl substituted with 0-5 R^5, C_3-C_{10} cycloalkyl substituted with 0-5 R^5, C_2-C_{10} alkenyl substituted with 0-5 R^5, or aryl substituted with 0-5 R^5;

R^2, R^3, and R^4 are each independently H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkenyl, benzyl, or phenyl; or R^3 and R^4 together form C_3-C_{10} cycloalkyl or C_3-C_{10} cycloalkenyl, optionally interrupted with O, S, NH, S(=O), $S(O)_2$, P(=O)(OH), C(=O)NH, NHC(=O), NHC(=O)NH, or NHC(=S)NH; and

each R^5 is independently H, NH_2, OH, CO_2H, $C(=O)NH_2$, C(=O)NHOH, $C(=O)NHNH_2$, $NHC(=NH)NH_2$, $NHC(=O)NH_2$, $NHC(=S)NH_2$, PO_3H_2, SO_3H, or $S(O)_2NH_2$

or a pharmaceutically acceptable salt thereof.

39. (Rejected; On Appeal) The composition of claim 38 wherein the second stabilizer is present at a concentration of about 0.1 mg/mL to about 20 mg/mL.

40. (Withdrawn) A method for preparing a stable radiopharmaceutical composition of claim 1 comprising:

combining in the absence of oxygen, the radiolabeled pharmaceutical agent of the formula (II):

$$RI\text{-}Ch\text{-}L_n(BM)_x \qquad (II);$$ and

an effective stabilizing amount of the stabilizer of the formula (I).

41. (Withdrawn) The method of claim 40 wherein the radiolabeled pharmaceutical agent and the stabilizer are combined in a container.

42. (Withdrawn) The method of claim 41 wherein an oxygen free head-space is maintained in the container.

43. (Withdrawn) The method of claim 40 further comprising cooling to a temperature of less than about -20°C.

44. (Withdrawn) The method of claim 40 further comprising storing to a temperature of less than about -20°C.

45. (Withdrawn) A method for preparing a stable radiopharmaceutical composition of claim 1 comprising:

combining in a container, in the absence of oxygen, the radiolabeled pharmaceutical agent of the formula $RI\text{-}Ch\text{-}L_n\text{-}(BM)_x$ and an effective stabilizing amount of the stabilizer of the formula (I);

maintaining an oxygen free head-space in the container;

cooling the container to a temperature of less than about -20° C; and

storing the container to a temperature of less than about -20°C.

46. (Withdrawn) A method for treating or preventing thromboembolic disorders, atherosclerosis, infection, inflammation, transplant rejection, cancer or a disease state that is associated with the following receptors: a cyclic IIb/IIIa receptor, a fibrinogen receptor, a myocardial receptor, a renal receptor, LTβ34, selectin, growth factor (PDGF, VEGF, BGF,

FGF, TNF MCSF or an interleukin I11-8), a receptor that is expressed or upregulated in angiogenic tumor vasculature, αvβ3, αvβ5, α5β1, α4β1, α1β1, or α2β2, α5β1, αvβ3, α5β1, or tyrosine kinases (e.g., epidermal growth factor receptor (EGFR) family in a mammalian tissue inflicted with or at risk thereof comprising contacting the mammalian tissue with an effective amount of a composition of claim 1.

47. (Withdrawn) The method of claim 46 wherein the mammal is a human.

48. (Withdrawn) The method of claim 46 wherein the contacting is *in vivo.*

49. (Withdrawn) The method of claim 46 wherein the contacting is *in vitro.*

50. (Withdrawn) A method for treating or preventing cancer,thromboembolic disorders, atherosclerosis, infection, inflammation, transplant rejection, cancer or a disease state that is associated with the following receptors: a cyclic IIb/IIIa receptor, a fibrinogen receptor, a myocardial receptor, a renal receptor, LTβ4, selectin, growth factor (PDGF, VBGF, EGF, FGF, TNF MCSF or an interleukin I11-8), a receptor that is expressed or upregulated in angiogenic tumor vasculature, αvβ3, αvβ5, α5β1, α4β1, α1β1, or α2β2, α5β1, αvβ3, α5β1 or tyrosine kinases (e.g., epidermal growth factor receptor (EGFR) family in a patient (e.g., mammal) inflicted with or at risk thereof comprising administering to the mammal in need of such treatment or prevention an effective amount of a composition of claim 1.

51. (Withdrawn) The method of claim 50 wherein the mammal is a human.

52. (Withdrawn) A method for imaging a tumor on or in a mammalian tissue inflicted with a tumor comprising contacting the mammalian tissue with an effective amount of a composition of claim 1; and detecting the presence of the radiolabeled pharmaceutical; wherein the ligand has an affinity for tumor cells.

53. (Withdrawn) The method of claim 52 wherein the mammal is a human.

54. (Withdrawn) The method of claim 52 wherein the contacting is *in vivo.*

55. (Withdrawn) The method of claim 52 wherein the contacting is *in vitro.*

56. (Withdrawn) A method for imaging a tumor in a mammal inflicted with a tumor comprising administering to the mammal an effective amount of a composition of claim 1; and detecting the presence of the radiolabeled pharmaceutical.

57. (Withdrawn) The method of claim 56 wherein the mammal is a human.

58. (Withdrawn) The method of claim 56 wherein the tumor is located in the breast, lung, thyroid, lymph node, kidney, ureter, bladder, ovary, teste, prostate, bone, skeletal muscle, bone marrow, stomach, esophagus, small bowel, colon, rectum, pancreas, liver, smooth muscle, brain, spinal cord, nerves, ear, eye, nasopharynx, oropharynx, salivary gland, or the heart.

59. (Withdrawn) A pharmaceutical composition of claim 1 for use in medical therapy or diagnosis.

60. (Withdrawn) The use of a pharmaceutical composition of claim 1 for the manufacture of a medicament for imaging or treating a tumor in a mammal.

61. (Withdrawn) The use of a pharmaceutical composition of claim 1 for the manufacture of a medicament for treating a tumor, a thromboembolic disorder, atherosclerosis, an infection, inflammation, transplant rejection or a disease state that is associated with the following receptors: a cyclic IIb/IIIa receptor, a fibrinogen receptor, a myocardial receptor, a renal receptor, LTβ4, selectin, growth factor (PDGF, VEGF, EGF, FGF, TNF MCSF or an interleukin I11-8), a receptor that is expressed or upregulated in angiogenic tumor vasculature, αvβ3, αvβ5, α5β1, α4β1, α1β1, or α2β2, α5β1, αvβ3, α5β1or tyrosine kinases (e.g., epidermal growth factor receptor (EGFR) family in a mammal.

62. (Withdrawn) A diagnostic composition comprising an effective diagnostic amount of a radiolabeled agent RI-Ch-Ln-$(BM)_x$, an effective stabilizing amount of a compound of formula (I) of claim 1, and a physiologically acceptable carrier or excipient.

63. (Withdrawn) A compound of formula (I) of claim 1 for use in preparing a stable radio-imaging composition comprising an effective diagnostic amount of a radiolabeled agent RI-Ch-Ln-$(BM)_x$, an effective stabilizing amount of a compound of formula (I) of claim 1, and a physiologically acceptable carrier or excipient.

64. (Withdrawn) A scintigraphic diagnostic composition comprising an effective stabilizing amount of a compound of formula (I)and a radiolabeled agent RI-Ch-Ln-$(BM)_x$ of claim 1.

65. (Withdrawn) A method of *in vivo* radio-imaging comprising:

(a) introducing a radioisotope (RI) to a solution comprising a compound Ch-Ln-$(BM)_x$ and an effective stabilizing amount of a compound of formula (I) of claim 1, to form a labeled solution;

(b) administering the labeled solution *in vivo;* and

(c) detecting localization of the radioisotope *in vivo.*

66. A method of *in vitro* radio-imaging a targeted receptor of a tissue comprising:

(a) administering an effective diagnostic amount of a composition according to claim 62 to the tissue; and

(b) detecting localization of the radiolabeled agent at the targeted receptor.

67. (Withdrawn) The method according to claim 66 wherein the targeted receptor is selected from the group consisting of a cyclic IIb/IIIa receptor, a fibrinogen receptor, a myocardial receptor, a renal receptor, LTβ4, selectin, growth factor (PDGF, VBGF, EGF, FGF, TNF MCSF or an interleukin I11-8), a receptor that is expressed or upregulated in angiogenic tumor vasculature, αvβ3, αvβ5, α5β1, α4β1, α1β1, or α2β2, α5β1, αvβ3, α5β1 and tyrosine kinases (e.g., epidermal growth factor receptor (EGFR) family.

68. (Withdrawn) A method of radio-imaging a targeted site within a patient's body comprising:

(a) administering an effective diagnostic amount of a composition according to claim 62 to the patient; and

(b) detecting localization of the radiolabeled agent at the targeted site.

69. (Withdrawn) A method of radio-imaging for prostate cancer or other tissues having an androgen receptor in a patient comprising:

(a) administering an effective diagnostic amount of a composition according to claim 62; and

(b) detecting the presence of the radiolabeled agent RI-Ch-Ln-$(BM)_x$ bound to the androgen receptor.

70. (Withdrawn) A method of radio-imaging metastasized cancer cells comprising contacting an effective diagnostic amount of a radiolabeled agent RI-Ch-Ln-$(BM)_x$ and an effective stabilizing amount of a compound of formula (I) of claim 1, with a composition comprising ST receptor wherein said radiolabeled agent is capable of targeting a ST receptor.

71. (Withdrawn) A method of radio-imaging a patient's organ comprising:

(a) administering an effective diagnostic amount of a radiolabeled agent RI-Ch-Ln-$(BM)_x$, and an effective stabilizing amount of a compound of formula (I) of claim 1 to a patient in need of such radioimaging; and

(b) and detecting the presence of the radiolabeled agent bound to said organ.

72. (Withdrawn) The method of claim 71 wherein the organ is selected from the group consisting of the breast, lung, thyroid, lymph node, kidney, ureter, bladder, ovary, teste, prostate, bone, skeletal muscle, bone marrow, stomach, esophagus, small bowel, colon, rectum, pancreas, liver, smooth muscle, brain, spinal cord, nerves, ear, eye, nasopharynx, oropharynx, salivary gland, and the heart.

73. (Withdrawn) A method of delivering a radionuclide to a target location, comprising: providing a radiolabeled agent RI-Ch-Ln-$(BM)_x$ and providing an effective stabilizing amount of a compound of formula (I) of claim 1.

74. (Withdrawn) The method of claim 73 wherein the target location is a cancer cell.

75. (Withdrawn) A kit for preparing a radio-imaging composition, the kit comprising a sealed vial containing a predetermined quantity of a radiolabeled agent RI-Ch-Ln-$(BM)_x$ and an effective stabilizing amount of a compound of formula (I) of claim 1.

76. (Withdrawn) A kit comprising a plurality-vial system of a radio-imaging composition of claim 62 and a diluent, comprising:

(a) a first vial comprising a predetermined quantity of a radiolabelled agent RI-Ch-Ln-$(BM)_x$ and an effective stabilizing amount of a compound of formula (I); and

(b) a second vial comprising a pharmaceutically acceptable carrier or diluent.

77. (Withdrawn) A pharmaceutical composition comprising a radiolabeled agent RI-Ch-Ln-$(BM)_x$, an effective stabilizing amount of a compound of formula (I) of claim 1, and optionally an effective stabilizing amount of a second stabilizer compound selected from the group consisting of of ascorbic acid, benzyl alcohol, gentisic acid, an ester of gentisic acid, gentisyl alcohol, an ester of gentisyl alcohol, *p*-aminobenzoic acid, cystamine, cystamine, 5-amino-2-hydroxybenzoic acid, nicotinic acid, nicotinamide, propylene glycol, dextran, inositol, a compound of formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

78. (Withdrawn) A method of preparing a stable radiopharmaceutical composition, comprising:

providing a radiolabeled agent RI-Ch-Ln-$(BM)_x$ and providing an effective stabilizing amount of a compound of formula (I) of claim 1.

79. (Withdrawn) A method of treating cancer, comprising administering to a patient, in need thereof, a therapeutically effective amount of a pharmaceutical composition according to claim 77 and optionally at least one agent selected from the group consisting of a chemotherapeutic agent and a radio sensitizer agent, or a pharmaceutically acceptable salt thereof.

80. (Withdrawn) The method according to claim 79 wherein administering is concurrent.

81. (Withdrawn) The method according to claim 79 wherein administering is sequential.

82. (Withdrawn) The method of treating cancer according to claim 79 wherein the cancer is a vascularized tumor (i.e. a solid tumor).

83. (Withdrawn) The method according to claim 79 wherein the cancer is selected from the group consisting of carcinomas of the lung, breast, ovary, stomach, pancreas, larynx, esophagus, testes, liver, parotid, biliary tract, colon, rectum, cervix, uterus, endometrium, kidney, bladder, prostate,thyroid, squamous cell carcinomas, adenocarcinomas, small cell carcinomas, melanomas, gliomas, and neuroblastomas.

84. (Withdrawn) The method according to claim 79 wherein the chemotherapeutic agent is selected from the group consisting of mitomycin, tretinoin, ribomustin, gemcitabine, vincristine, etoposide, cladribine, mitobronitol, methotrexate, doxorubicin, carboquone, pentostatin, nitracrine, zinostatin, cetrorelix, letrozole, raltitrexed, daunorubicin, fadrozole, fotemustine, thymalfasin, sobuzoxane, nedaplatin, cytarabine, bicalutamide, vinorelbine, vesnarinone, aminoglutethimide, amsacrine, proglumide, elliptinium acetate, ketanserin, doxifluridine, etretinate, isotretinoin, streptozocin, nimustine, vindesine, flutamide, drogenil, butocin, carmofur, razoxane, sizofilan, carboplatin, mitolactol, tegafur, ifosfamide, prednimustine, picibanil, levamisole, teniposide, improsulfan, enocitabine, lisuride, oxymetholone, tamoxifen, progesterone, mepitiostane, epitiostanol, formestane, interferon-alpha, interferon-2 alpha, interferon-beta, interferon-gamma, colony stimulating factor- 1, colony stimulating factor-2, denileukin diftitox, interleukin-2, and leutinizing hormone releasing factor.

85. (Withdrawn) The method according to claim 79 wherein the radiosensitizer agent is selected from the group consisting of 2-(3-nitro-1,2,4-triazol- 1 -yl)-N-(2-methoxyethyl)acetamide, N-(3 -nitro-4-quinolinyl)-4-morpholinecarboxamidine, 3-amino-1,2,4-benzotriazine- 1,4-dioxide, N-(2-hydroxyethyl)-2-nitroimidazole-1-acetamide, 1-(2-nitroimidazol-1-yl)-3-(1-piperidinyl)-2-propanol, and 1-(2-nitro- 1 -imidazolyl)-3-(1-aziridino)-2-propanol.

86. (Withdrawn) A kit for treating cancer, comprising a therapeutically effective amount of a pharmaceutical composition according to claim 77 and optionally at least one agent

selected from the group consisting of a chemotherapeutic agent and a radiosensitizer agent,or a pharmaceutically acceptable salt thereof.

87. (Withdrawn) The kit according to claim 86 wherein said kit comprises a plurality of separate containers, wherein at least one of said containers contains a therapeutically effective amount of a pharmaceutical composition according to claim 77, and at least another of said containers contains one or more agents selected from the group consisting of a chemotherapeutic agent and a radiosensitizer agent, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

88. (Withdrawn) The kit according to Claim 86, wherein the chemotherapeutic agent is selected from the group consisting of mitomycin, tretinoin, ribomustin, gemcitabine, vincristine, etoposide, cladribine, mitobronitol, methotrexate, doxorubicin, carboquone, pentostatin, nitracrine, zinostatin, cetrorelix, letrozole, raltitrexed, daunorubicin, fadrozole, fotemustine, thymalfasin, sobuzoxane, nedaplatin, cytarabine, bicalutamide, vinorelbine, vesnarinone, aminoglutethimide, amsacrine, proglumide, elliptinium acetate, ketanserin, doxifluridine, etretinate, isotretinoin, streptozocin, nimustine, vindesine, flutamide, drogenil, butocin, carmofur, razoxane, sizofilan, carboplatin, mitolactol, tegafur, ifosfamide, prednimustine, picibanil, levamisole, teniposide, improsulfan, enocitabine, lisuride, oxymetholone, tamoxifen, progesterone, mepitiostane, epitiostanol, formestane, interferon-alpha, interferon-2 alpha, interferon-beta, interferon-gamma, colony stimulating factor-1, colony stimulating factor-2, denileukin diftitox, interleukin-2, and leutinizing hormone releasing factor.

89. (Withdrawn) The kit according to Claim 86, wherein the chemotherapeutic agent is selected from the group consisting of mitomycin, tretinoin, ribomustin, gemcitabine, vincristine, etoposide, cladribine, mitobronitol, methotrexate, doxorubicin, carboquone, pentostatin, nitracrine, zinostatin, cetrorelix, letrozole, raltitrexed, daunorubicin, fadrozole, fotemustine, thymalfasin, sobuzoxane, nedaplatin, cytarabine, bicalutamide, vinorelbine, vesnarinone, aminoglutethimide, amsacrine, proglumide, elliptinium acetate, ketanserin, doxifluridine, etretinate, isotretinoin, streptozocin, nimustine, vindesine, flutamide, drogenil, butocin, carmofur, razoxane, sizofilan, carboplatin, mitolactol, tegafur,

ifosfamide, prednimustine, picibanil, levamisole, teniposide, improsulfan, enocitabine, and lisuride.

90. (Withdrawn) The kit according to Claim 86 wherein the chemotherapeutic agent is selected from the group consisting of oxymetholone, tamoxifen, progesterone, mepitiostane, epitiostanol, and formestane.

91. (Withdrawn) The kit according to Claim 86 wherein the chemotherapeutic agent is selected from the group consisting of interferon-alpha, interferon-2 alpha, interferon-beta, interferon-gamma, colony stimulating factor-1, colony stimulating factor-2, denileukin diflitox, interleukin-2, and leutinizing hormone releasing factor.

92. (Withdrawn) The kit according to Claim 86, wherein the radiosensitizer agent is selected from the group consisting of 2-(3-nitro-1,2,4-triazol-1-yl)-N-(2-methoxyethyl)acetamide, N-(3-nitro-4-quinolinyl)-4-morpholinecarboxamidine, 3-amino-1 ,2,4-benzotriazine- 1,4-dioxide, N-(2-hydroxyethyl)-2-nitroimidazole-1 -acetamide, 1 -(2-nitroimidazol- 1 -yl)-3 -(1 -piperidinyl)-2-propanol, and 1 -(2-nitro- 1 -imidazolyl)-3-(1 -aziridino)-2-propanol.

10. LIST OF REFERENCES

U.S. Patent No. 6,537,520 to Rajopadhye *et al.*

U.S. Patent No. 5,679,318 to Vanderheyden *et al.*

Japanese Patent No. JP 56144060 (Abstract attached to back)

U.S. Patent No. 5,750,088 to Sworin *et al.*

U.S. Patent No. 5,707,603 to Toner *et al.*

Date: Dec. 9, 2004

Brian J. Hubbard
Registration No. 45,873

Woodcock Washburn LLP
One Liberty Place - 46th Floor
Philadelphia PA 19103
Telephone: (215) 568-3100
Facsimile: (215) 568-3439

⑲ 日本国特許庁（JP）　　⑪ 特許出願公開

⑫ 公開特許公報（A）　　昭56—144060

⑤1Int. Cl.³　識別記号　庁内整理番号　⑬公開　昭和56年(1981)11月10日
A 23 K　3/00　7803—2B

発明の数　1
審査請求　未請求

（全 3 頁）

---

⑤4飼料用酸化防止剤

⑦1出　願　人　千葉市長沼町269—20—24—704
日本油脂株式会社
東京都千代田区有楽町1丁目10番1号

⑦1特　願　昭55—47246
⑦2出　願　昭55(1980)4月10日
⑦2発　明　者　吉永晴雄

明　細　書

1　発明の名称

飼料用酸化防止剤

2　特許請求の範囲

没食子酸70～99重量%とL－アスコルビン酸1～30重量%とからなる飼料用酸化防止剤

3　発明の詳細な説明

本発明は、鉄と接触しても着色せず、しかも、抗酸化性にすぐれた飼料用酸化防止剤（以下単に酸化防止剤という）に関するものである。

従来、酸化防止剤としてエトキシキン（6－エトキシ－1，2－ジヒドロ－2，2，4－トリメチルキノリン）が主に使用されているが、毒性が強く、しかも、相当多量に添加しないと効果がないなどの欠点を有するため、安全でしかも強力な酸化防止剤の開発が望まれていた。

一方、没食子酸は、抗酸化性を有することが知られているが、鉄と接触して青色ないし黒色に着色するという欠点があった。

本発明者は、没食子酸が植物の成分であるタンニン酸を加水分解して得られる衛生上安全な物質であること、および強い抗酸化性を有することに着目し、多年研究の結果、没食子酸が油脂に適量溶解すること、没食子酸とL－アスコルビン酸とを混合すれば鉄と接触しても着色しないこと、および両者の混合により抗酸化性に対する相乗効果が得られることの知見を得、エトキシキンよりも強力な酸化防止剤の開発に成功した。

L－アスコルビン酸以外の有機酸にも、没食子酸と混合することにより抗酸化性に対する相乗効果を示すものもあるが、第1表に示すようにL－アスコルビン酸が最も効果的であり、さらに、着色防止効果も、第2表に示すようにL－アスコルビン酸が最もすぐれている。

第　1　表

抗酸化性に対する相乗効果

酸化防止剤	精製豚脂のAOM(時間)
無添加	4.5
没食子酸100%	102
没食子酸95%＋リンゴ酸　5%	104
没食子酸90%＋リンゴ酸　10%	96
没食子酸95%＋クエン酸　5%	105
没食子酸90%＋クエン酸　10%	98
没食子酸95%＋L-アスコルビン酸　5%	132
没食子酸90%＋L-アスコルビン酸10%	102

（注）(1)%：重量%

(2)試験方法：精製豚脂に0.002重量%の酸化防止剤を添加してＡＯＭを測定した。

第　2　表

没食子酸に対する着色防止効果

酸化防止剤中の有機酸の重量比(%) ＼ 有機酸	0.5	1	5	10	30	50	70
リンゴ酸	+++	+++	+++	+++	+++	+++	+++
クエン酸	+++	+++	+++	+++	+++	++	+
Ｌ－アスコルビン酸	+	±	-	-	-	-	-

（注）(1) +++ ：かなり濃い着色

++ ：濃い着色

+ ：薄い着色

± ：かすかに着色

- ：着色せず

(2)試験方法：酸化防止剤の1%水溶液100mℓに1%塩化第2鉄水溶液2mℓを加え、着色の程度を目視により判定した。

本発明の酸化防止剤は、没食子酸70～99重量%とＬ－アスコルビン酸1～30重量%とからなるものである。

本発明に用いる没食子酸としては、加水分解性のタンニン酸から得られる天然のものが市販されており、含水量の少ない粉末状のものがよい。

また、Ｌ－アスコルビン酸は、微粉末状のものをそのまま用いる。

Ｌ－アスコルビン酸は、没食子酸の鉄による着色防止のために1重量%以上混合する必要があるが、30重量%を越えると相対的に没食子酸量が少くなり、抗酸化性が低下するので好ましくない。着色をより完全に防止するためには、3～30重量%混合するのが好ましい。

本発明の酸化防止剤は、没食子酸とＬ－アスコルビン酸との2成分を単に混合することにより得られる。

本発明の酸化防止剤は、飼料用原料油脂または配合飼料そのものに添加して用いる。飼料用原料油脂に添加するときは、50～60℃に加温、融解した油脂に粉末のまま添加すればよいが、酸化防止剤をエタノールに溶解してから添加すればなお速やかに油脂中に溶ける。また、配合飼料などに直接添加する場合は、酸化防止剤を粉体状の吸着剤と混合してから飼料と混合するか、または、エタノールに溶解したのち、飼料に噴霧すればよい。添加量は、飼料用原料油脂に対しては50～200ppm、配合飼料に対しては10～100ppmが適当である。

本発明の酸化防止剤を飼料用原料油脂または配合飼料に添加することにより、飼料に含まれる油脂の劣化が完全に防止され、従来用いられていたエトキシキンの約1/3の添加量でエトキシキンと同等の抗酸化性が得られる。しかも、没食子酸は、前述のとおり衛生上安全な天然物を原料とするものであり、一方、Ｌ－アスコルビン酸は、別名ビタミンＣで知られるように飼料の栄養強化に役立つものである。また、本発明の酸化防止剤は、没食子酸とＬ－アスコルビン酸とを単に混合するだけという簡単な手順で比較的安価に製造できるの

で、飼料に用いる酸化防止剤として極めて有益なものである。

次に、本発明を実施例によつて説明し、その有益性を明確にする　実施例において%は重量%を表わす。

実施例1

EF牛脂に、エトキシキン0.01%、0.03%、0.05%、本発明の酸化防止剤（没食子酸95%、L－アスコルビン酸5%の混合物）0.01%、0.02%、0.05%をそれぞれ添加した試料油を調製し、AOM安定度（加熱温度97.8±1℃、通気量2.33ml／秒）を測定した。過酸化物価の経時変化を比較した結果を第3表に示す。

第3表

酸化防止剤	添加量(%)	過酸化物価			
		10時間後	20時間後	30時間後	100時間後
エトキシキン	0.01	300			
〃	0.03	30	300		
〃	0.05	10	16	20	400
本発明品	0.01	9	17	28	400
〃	0.02	6.5	12	17	300
〃	0.05	4.0	4.0	4.5	5.7

第3表の結果から明らかなように、本発明の酸化防止剤を添加したEF牛脂は、過酸化物価の上昇程度が少なく、本発明の酸化防止剤はエトキシキンに比べて著しくすぐれた抗酸化性を示すことがわかる。

なお、本発明の酸化防止剤を添加した各試料について着色試験を実施したところ、いずれも着色は見られなかつた。

実施例2

60℃に加温したYG牛脂に、エトキシキン0.05%、BHA0.02%、本発明の酸化防止剤（没食子酸75%、L－アスコルビン酸25%の混合物）0.015%および0.05%をそれぞれ添加し、5分間撹拌して試料油を調製した。各試料油および比較品としての酸化防止剤無添加の試料油それぞれ15gを直径8.5cmのシャーレに入れ、60℃の恒温室内（暗所）に静置し、1カ月、2カ月、3カ月後の過酸化物価を測定した。結果を第4表に示す。

第4表

酸化防止剤	添加量(%)	過酸化物価			
		調製時	1カ月後	2カ月後	3カ月後
無添加	—	2.0	12.0	20.5	350
BHA	0.02	2.0	10	10.5	18.0
エトキシキン	0.05	2.0	4.5	4.5	5.0
本発明品	0.015	2.0	4.0	4.5	5.0
本発明品	0.05	2.0	2.5	2.5	2.5

第4表に示したように、本発明の酸化防止剤を添加したYG牛脂は、長期間保存しても過酸化物価の上昇がほとんどなく極めて安定で、本発明の酸化防止剤がすぐれていることがわかる。

なお、本発明の酸化防止剤を添加した各試料について着色試験を実施したところ、いずれも着色はまつたく見られなかつた。

特許出願人　日本油脂株式会社

POWERED BY Dialog

Antioxidant for oil and fat used in foodstuff - comprises gallic acid and L-ascorbic acid
Patent Assignee: NIPPON OILS & FATS CO LTD

Patent Family

Patent Number	Kind	Date	Application Number	Kind	Date	Week	Type
JP 56144060	A	19811110				198151	B
JP 82059739	B	19821216				198303	
FR 2513491	A	19830401				198318	

Priority Applications (Number Kind Date): JP 8047246 A (19800410)

Patent Details

Patent	Kind	Language	Page	Main IPC	Filing Notes
JP 56144060	A		3		

Abstract:
JP 56144060 A

Antioxidant for feed use is composed of 70-99 w/w% of gallic acid and 1-30 w/w% of L-ascorbic acid.

The antioxidising activity of antioxidant is stronger than that of 6-ethoxy-1,2-dihydro-2,2, 4-trimethyl-quinoline and the amt. of the antioxidant for attaining similar antioxidising effect as Ethoxyquin can be decreased to ca. 1/3. Usually the antioxidant is combined 50-200 ppm in the starting oil and fat of feed use and 10-100 ppm in assorted feeds.

By combining L-ascorbic acid in gallic acid, the discolouration with iron can be prevented, and also the antioxidising activity of gallic acid is synergically intensified. Oxidn. of the oil and fat in feed, can be prevented.

ANTIOXIDANT FOR FEED

Publication Number: 56-144060 (JP 56144060 A) , November 10, 1981

Inventors:
- YOSHINAGA HARUO

Applicants

- NIPPON OIL & FATS CO LTD (A Japanese Company or Corporation), JP (Japan)

Application Number: 55-047246 (JP 8047246) , April 10, 1980

International Class (IPC Edition 3):

- A23K-003/00

JAPIO Class:

- 11.3 (AGRICULTURE--- Livestock)

Abstract:
PURPOSE: Gallic acid and L-ascorbic acid are included in a specific proportion to give an antioxidant for feed that is free from coloring, even when it comes into contact with iron, and shows high antioxdative property.

CONSTITUTION: A powder of gallic acid, preferably of low water content, (70- 99wt%) is mixed with a fine powder of L-ascorbic acid. The anitoxidant is added to a fat for feed by about 50-20ppm or to formulated feed by about 10-100ppm. (From: *Patent Abstracts of Japan*, Section: C, Section No. 90, Vol. 06, No. 19, Pg. 159, February 03, 1982)